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Review

Comparative meta-analysis of adefovir dipivoxil monotherapy and combination therapy of adefovir dipivoxil and lamivudine for lamivudine-resistant chronic hepatitis B

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SUMMARY

Objectives: The aim of the current study was to compare the effectiveness of adefovir dipivoxil (ADV) monotherapy with that of combination ADV and lamivudine (LAM) therapy in the treatment of LAM-resistant chronic hepatitis B (CHB).

Methods: Publications on the effectiveness of ADV monotherapy versus the combination of ADV and LAM therapy for the treatment of LAM-resistant CHB were identified by a search (up to year 2010) of the PubMed, HealthStar, ScienceDirect, and VIP databases. Biochemical response data (alanine aminotransferase normalization rate) and virological response data (serum hepatitis B virus DNA undetectable rate) were extracted and combined to obtain an integrated result.

Results: The literature search yielded 11 articles, six of which reported randomized controlled trials; the remaining five reported prospective cohort studies. The summary odds ratio (OR) values of the biochemical response at 3, 6, 12, and >12 months were 1.60 ($p = 0.06$), 1.30 ($p = 0.18$), 1.77 ($p = 0.008$), and 3.35 ($p < 0.00001$), respectively. The summary OR values of the virological response at 3, 6, 12, and >12 months were 1.46 ($p = 0.21$), 1.68 ($p = 0.04$), 1.16 ($p = 0.54$), and 1.87 ($p = 0.01$), respectively.

Conclusions: The effectiveness of the combination therapy was not obviously predominant over the monotherapy in short duration therapies; however, the combination therapy had a great advantage over monotherapy in both biochemical and virological response when the therapy duration was prolonged to >12 months.

1. Introduction

Chronic hepatitis B (CHB) is prevalent, with an estimated 350 million cases worldwide.[1] Despite the availability of vaccines to immunize people against the disease, CHB remains a major health problem in many countries because of its high degree of infectiousness.[2,3]

Antiviral medication plays an important role in the treatment of CHB.[4,5] Anti-hepatitis B virus (HBV) therapy can postpone the spread of the disease, enhance patient quality of life, and prolong the patient's life span.[5] In recent years, the prognosis and clinical history of chronic HBV infection have been changed by antiviral therapies.[6,7] One such type of antiviral medication, the nucleotide analogues, are becoming increasingly popular because they are administered orally, there is an observable efficacy in the treatment of disease, and the adverse reaction rate is low.

Drug resistance is a major problem for nucleotide analogues during antiviral therapy. Therefore, another drug is usually added to the current medication, or the ongoing drug is switched to another medication.[8,9] Lamivudine (LAM) was the first commonly used nucleotide analogue. However, LAM resistance in patients is now prevalent. The second nucleotide analogue introduced to the market was adefovir dipivoxil (ADV). ADV can effectively inhibit the replication of HBV DNA and can therefore be used for LAM-resistant patients. The meta-analysis presented in this paper was undertaken in order to determine whether adding ADV to ongoing LAM treatment or switching LAM to ADV is the better therapy option.

2. Methods

2.1. Literature search

The retrieval of articles in the English-language literature was conducted by a search of the ScienceDirect, PubMed, and HealthStar databases; articles in the Chinese-language literature were identified by a VIP database search. Articles published up

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Table 1
Basic information about the study

Study number	The study [Ref.]	Research design	The age of patients	Study duration	Treatment protocols	Sample size
1	Yang et al., 2008 [10]	RCT	l6–62	48 weeks	Monotherapy	73
					Combination therapy	73
2	Luo 2009 [11]	RCT	19–56	1 year	Monotherapy	21
					Combination therapy	21
3	Zhan et al., 2009 [12]	RCT	18–65	72 weeks	Monotherapy	42
					Combination therapy	38
4	Gaia et al., 2008 [13]	Prospective cohort study	>18	72 months	Monotherapy	29
					Combination therapy	23
5	Vassiliadis et al., 2009 [14]	RCT	>18	60 months	Monotherapy	15
					Combination therapy	45
6	Rapti et al., 2007 [15]	RCT	>18	4 years	Monotherapy	14
					Combination therapy	28
7	Peters et al., 2004 [16]	RCT	16–65	48 weeks	Monotherapy	19
					Combination therapy	20
8	Fung et al., 2007 [17]	Prospective cohort study	>15	24 months	Monotherapy	28
					Combination therapy	28
9	Santantonio et al., 2009 [18]	Prospective cohort study	>18	55 months	Monotherapy	30
					Combination therapy	30
10	Kim et al., 2005 [19]	Prospective cohort study	18–67	24 weeks	Monotherapy	18
					Combination therapy	28
11	Manolakopoulos et al., 2007 [20]	Prospective cohort study	>18	48 months	Monotherapy	23
					Combination therapy	59

RCT, randomized controlled trial.

until the year 2010 were included. The search protocols used combinations of the following keywords: "Lamivudine", "Adefovir Dipivoxil", and "Chronic Hepatitis B". Titles and abstracts were screened to determine the relevance of the articles. Next, the article full-texts were reviewed. Abstracts, case reports, editorials, and review articles were excluded from the meta-analysis. The literature search was carried out by two different individuals.

2.2. Inclusion and exclusion criteria

The inclusion criteria for the present study were the following: (1) all patients with diagnosed CHB, ongoing LAM therapy, and who had developed LAM resistance, (2) studies comparing the effectiveness of ADV monotherapy with that of combination ADV and LAM therapy, (3) randomized controlled trials (RCTs) or prospective cohort studies, and (4) virological or biochemical response data.

Exclusion criteria were as follows: case report; review; editorial; non-comparative study; retrospective study; non-English or non-Chinese; co-infection with other viruses; liver transplantation; hepatic cirrhosis; non-LAM resistance; no intervention; usage of other drugs; and other articles irrelevant to the objectives of the present study.

2.3. Quality assessment and data extraction

The quality of the studies was assessed using the following factors: (1) definite description of the methods employed, including the inclusion criteria for patients, grouping and treatment, follow-up treatments, end-points, and statistical analyses, and (2) concrete presentation of results. Only those studies that fulfilled the above quality criteria were included in the meta-analysis.

Basic information about the studies was extracted, such as author's name, publication year, research design, study duration, and sample size (Table 1[10–20]). To determine the effectiveness of the therapy, biochemical response data (alanine aminotransferases normalization rate) and virological response data (serum HBV DNA undetectable rate) were also extracted.

Both quality assessment and data extraction were conducted by two different individuals.

2.4. Statistical analysis

The statistical analysis was conducted using Review Manager 5 software. The outcomes – biochemical response and virological response at 3, 6, 12, and >12 months after therapy – were evaluated using odds ratios (OR) and the 95% confidence intervals (95% CI).

The above software can automatically generate forest plots. The presence of heterogeneity was observed in the forest plots generated. At $p \geq 0.05$, heterogeneity was considered statistically insignificant, and the fixed effect model was used in the analysis. At $p < 0.05$, heterogeneity was considered statistically significant, and the random effect model was used in the analysis. The fixed effect model assumes identical treatment effects in the studies, whereas the random effect model assumes that each study has a unique treatment effect distributed randomly regarding an average study treatment effect.

In the forest plots generated, the integrated results are shown to the right, and the horizontal lines represent confidence intervals. The horizontal lines are longer when the sampling size is smaller. The square in the middle of the horizontal line represents the point estimation value for each study, and the solid diamond symbol represents the comprehensive effect of these studies. The vertical line divides the graph into two parts. When the result is unfavorable, the symbol on the left of the vertical line displays a better outcome. When the symbol and the vertical line intersect, no significant statistical difference exists between the two therapies.

2.5. Sensitivity analysis

Sensitivity analyses were conducted from two aspects to observe the effect of the following indeterminate factors: (1) Inclusion of RCTs only: only RCTs being included can control the heterogeneity well, so in the sensitivity analysis we determined what the outcomes would be if only the 6 RCTs were included. (2) Analysis using the random effect model as a substitute for the fixed effect model: the random effect model is typically applied when the studies included are evidently heterogeneous. In the baseline research, the fixed effect model was used because of the

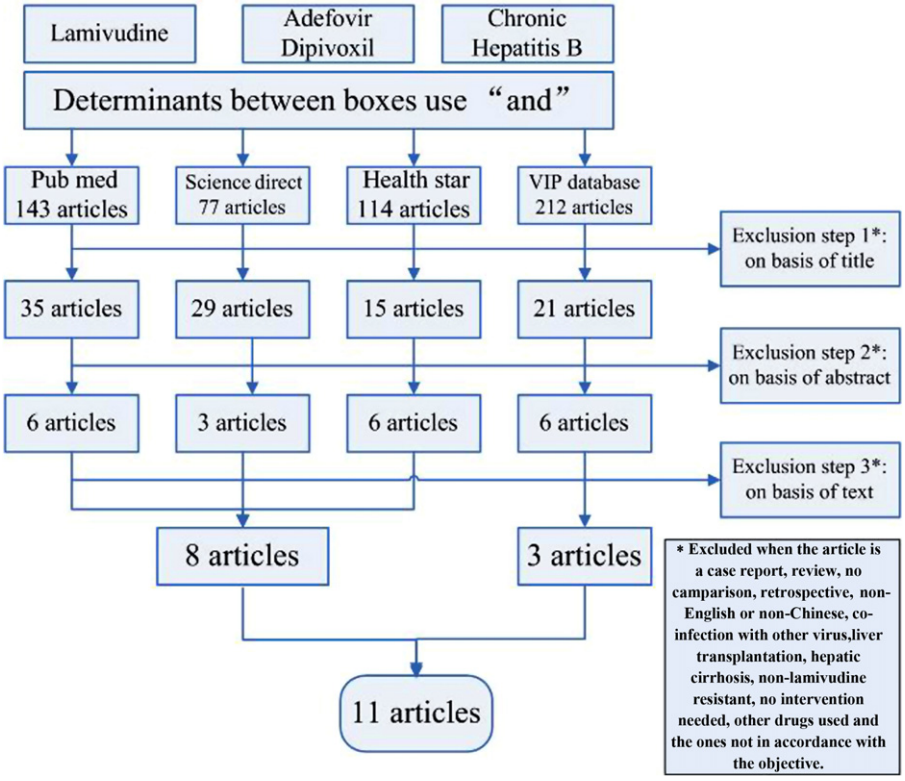


Figure 1. Search strategy flow chart and rationale for study exclusion.

heterogeneity of test results. The random effect model was used in the sensitivity analysis to minimize the potential effect of heterogeneity.

3. Results

3.1. Study selection and characteristics

The search method identified 143 articles from PubMed, 77 from ScienceDirect, 114 from HealthStar, and 212 from the VIP database. Articles with titles obviously not encompassing the selection criteria were excluded, including 108 from PubMed, 48 from ScienceDirect, 99 from HealthStar, and 191 from VIP. From the remaining publications, 29 PubMed, 26 ScienceDirect, 9 HealthStar, and 15 VIP articles were excluded based on their abstracts. The full text of the remaining articles was then read. Another seven English-language and three Chinese-language publications were excluded. In total, eight English-language and three Chinese-language studies were included. Of these 11 studies, six were RCTs (three each in Chinese and English), and the remaining five were prospective cohort studies (all in English). The screening process is shown in Figure 1, and details of the articles selected are shown in Table 1.

3.2. Meta-analysis

3.2.1. Biochemical response

From the forest plots (Appendices 1–4), no significant statistical heterogeneity was observed in all the studies in each subgroup. Therefore, the fixed effect model was used in the analysis. Based on the OR, 95% CI, and *p*-values, no significant difference was present between the monotherapy and combination therapy in terms of biochemical response after 3 and 6 months of therapy. However, prolonging the duration of therapy to ≥12 months revealed significant differences between the two therapies (Table 2).

3.2.2. Virological response

From the forest plots (Appendices 5–8), no significant statistical heterogeneity was present in all the studies in each subgroup, Thus, the fixed effect model was used in the analysis. Based on the OR, 95% CI, and *p*-values, no significant differences were present between the monotherapy and combination therapy in terms of

Table 2
Biochemical response results

Follow-up time (months)	Number of studies	*p*-Value of heterogeneity test	Model used	Results		OR (95% CI)	*p*-Value
				Monotherapy group, *n/N*	Combination therapy group, *n/N*		
3	4	0.48	Fixed effect model	48/132	72/147	1.60 (0.98, 2.61)	0.06
6	7	0.55	Fixed effect model	120/218	176/274	1.30 (0.89, 1.89)	0.18
12	7	0.71	Fixed effect model	142/217	200/257	1.77 (1.16, 2.70)	0.008
>12 (mean 50, median 52)	6	0.84	Fixed effect model	96/147	185/216	3.35 (1.96, 5.72)	<0.00001

OR, odds ratio; 95% CI, 95% confidence interval.

Table 3
Virological response results

Follow-up time (months)	Number of studies	*p*-Value of heterogeneity test	Model used	Results		OR (95% CI)	*p*-Value
				Monotherapy group, *n/N*	Combination therapy group, *n/N*		
3	2	0.07	Fixed effect model	27/86	45/113	1.46 (0.81, 2.62)	0.21
6	5	0.84	Fixed effect model	57/117	102/170	1.68 (1.02, 2.79)	0.04
12	6	0.61	Fixed effect model	75/146	113/193	1.16 (0.72, 1.88)	0.54
>12 (mean 46, median 48)	7	0.22	Fixed effect model	104/175	177/236	1.87 (1.16, 3.02)	0.01

OR, odds ratio; 95% CI, 95% confidence interval.

virological response after 3, 6, and 12 months of therapy. However, prolonging the therapy duration to >12 months revealed a significant difference between the two therapies (Table 3).

3.3. Sensitivity analysis

3.3.1. Inclusion of RCTs only – biochemical response

In the biochemical response research, three studies were included at 3 months of therapy, four at 6 months of therapy, five at 12 months of therapy, and three at >12 months of therapy. All the *p*-values of heterogeneity were >0.05, therefore the fixed effect model was used in the analysis. The summary OR, 95% CI, and *p*-values were 1.83 (1.06, 3.16), $p = 0.03$ at 3 months after therapy; 1.53 (0.97, 2.41), $p = 0.07$ at 6 months; 1.82 (1.12, 2.95), $p = 0.02$ at 12 months; and 4.39 (2.04, 9.46), $p = 0.0002$ at >12 months. The combination therapy did not show any considerable advantage during the first year of therapy. However when the therapy duration was extended to ≥12 months, the combination therapy appeared to be much more effective than the monotherapy.

3.3.2. Inclusion of RCTs only – virological response

In the virological response research, two studies were included at 3 months of therapy, three at 6 months of therapy, four at 12 months of therapy, and four at >12 months of therapy. All the *p*-values of heterogeneity were >0.05, therefore the fixed effect model was used in the analysis. The summary OR, 95% CI, and *p*-values were 1.46 (0.81, 2.62), $p = 0.21$ at 3 months; 0.96 (0.52, 1.78), $p = 0.90$ at 6 months; 1.46 (0.80, 2.63), $p = 0.21$ at 12 months; and 2.81 (1.49, 5.30), $p = 0.001$ at >12 months. No significant differences were found between the two therapies during the first year. However, when the therapy duration was extended to >12 months, the combination therapy seemed to be much more effective than the monotherapy.

3.3.3. Analysis using the random effect model as a substitute for the fixed effect model – biochemical response

Analysis using the random effect model produced the following summary of the OR, 95% CI, and *p*-values: 1.60 (0.97, 2.62), $p = 0.06$ at 3 months; 1.30 (0.88, 1.92), $p = 0.18$ at 6 months; 1.79 (1.17, 2.74), $p = 0.007$ at 12 months; and 3.40 (1.99, 5.81), $p < 0.00001$ at >12 months. The combination therapy did not exhibit any significant advantages during the first 6 months of therapy. However, when the therapy duration was extended to ≥12 months, the combination therapy appeared to be much more effective than the monotherapy.

3.3.4. Analysis using the random effect model as a substitute for the fixed effect model – virological response

Analysis using the random effect model yielded the following summary of the OR, 95% CI, and *p*-values: 1.91 (0.51, 7.08), $p = 0.34$ at 3 months; 1.10 (0.60, 2.00), $p = 0.76$ at 6 months; 1.17 (0.72, 1.91), $p = 0.53$ at 12 months; and 1.88 (1.03, 3.44), $p = 0.04$ at >12 months. No significant differences between the combination therapy and monotherapy were found. However, there was a trend showing that when the therapy duration went beyond 12 months, the combination therapy would be much more effective than the monotherapy.

4. Discussion

4.1. Summary of the analyses

Based on the baseline and sensitivity analyses, prolonging the duration of therapy to over 12 months results in a more favorable outcome for the combination therapy compared with the monotherapy. This result may be partly attributed to the wild-type HBV that emerges with time after the discontinuation of LAM, and in the combination therapy group LAM can help in decreasing the potential development of wild-type HBV. The Clinical Practice Guidelines for HBV of both the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases suggest the addition of adefovir (if tenofovir is not yet available) for LAM-resistant rescues. This recommendation is based on the antiviral effect and the risk of multiple drug-resistant strains. To some extent the current meta-analysis confirms the above guidelines.

4.2. Limitations

4.2.1. Quality of the studies included

From the 11 articles included in the present study, only six were RCTs, and no concrete descriptions were given about the methods of randomization. Five of the selected articles were prospective cohort studies, which may have more practical importance but will unavoidably induce heterogeneity. Moreover, the sample size in the studies included was not sufficiently large. Statistically, this was not persuasive enough to yield conclusive results.

4.2.2. Data extraction

The time units of the results provided in the studies were different, such as weeks, months, and even years. In the present research, all units of time were unified to months. Data were extracted for 3, 6, 12, and >12 months of therapy. In the extraction process, 48 and 52 weeks of treatment duration in the different studies were considered equal to 12 months. However, this method may also be a source of heterogeneity.

4.2.3. Inclusion criteria

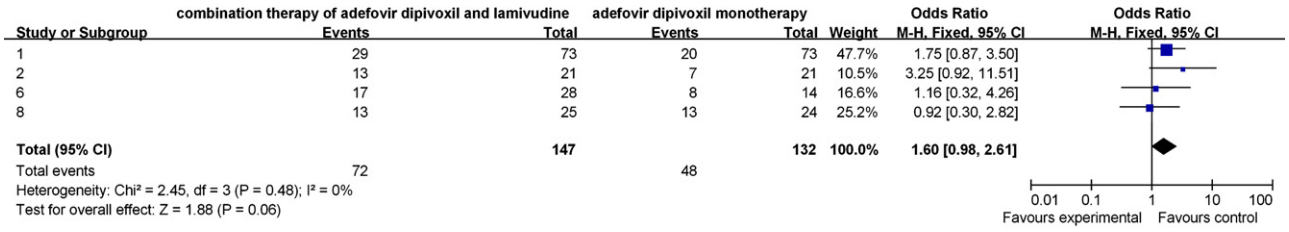
Several variations were included in the articles analyzed. In some studies, only LAM-resistant patients with hepatitis B e antigen (HBeAg)-negative CHB were included, whereas in others, only LAM-resistant patients with HBeAg-positive CHB were included, and other studies did not specify HBeAg status. This could also be a source of heterogeneity. However, the heterogeneity test results indicated that conducting any subgroup analysis was not necessary.

5. Conclusions

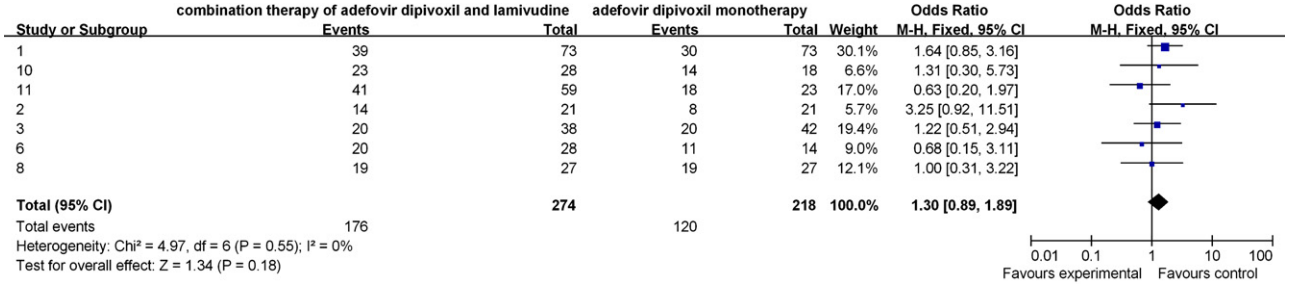
In conclusion, the results show that the effectiveness of both therapies depends on the duration of therapy. In therapies of short duration, no considerable predominance was observed for either therapy. However, extending therapy to more than 12 months gave the combination therapy a greater advantage over monotherapy, both in terms of biochemical and virological response.

Conflict of interest: The current study was completed by the authors without any support from other organizations. No conflict of interest to declare.

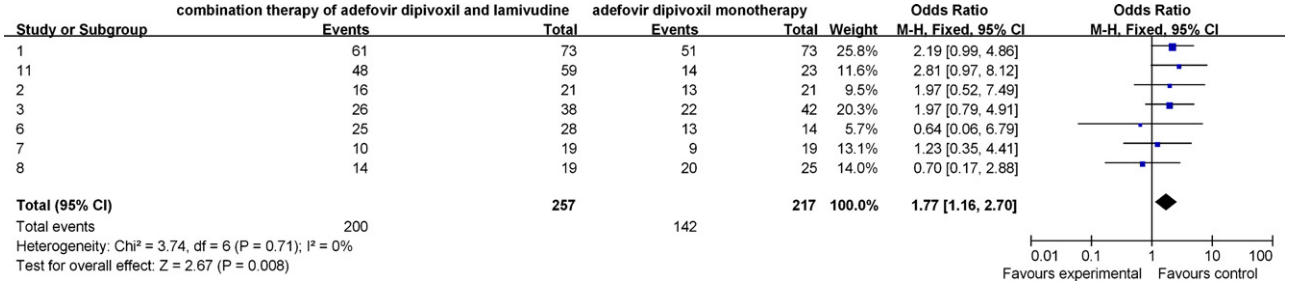
Appendix 1. Forest plot for biochemical response after 3 months of therapy.



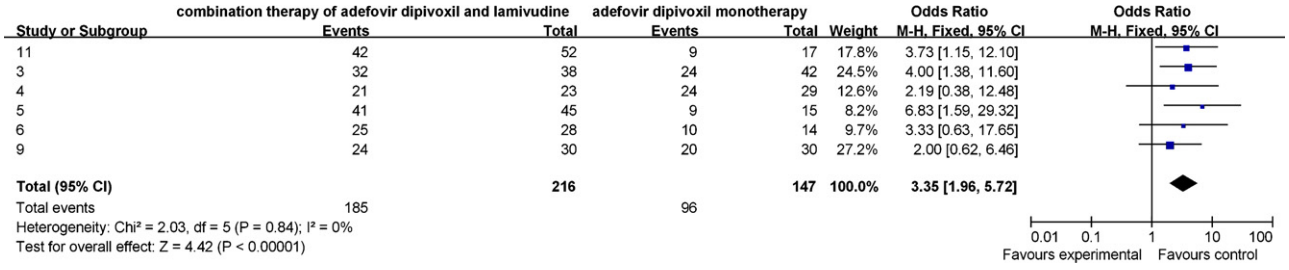
Appendix 2. Forest plot for biochemical response after 6 months of therapy.



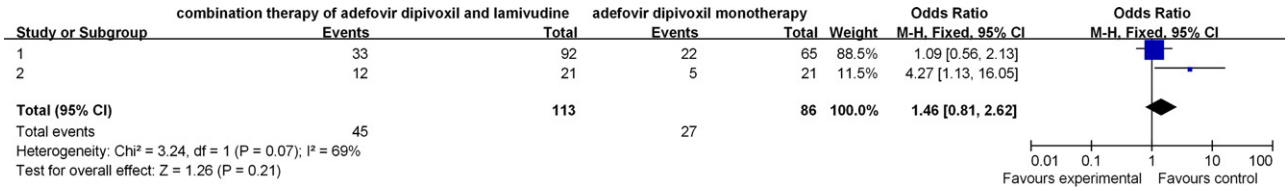
Appendix 3. Forest plot for biochemical response after 12 months of therapy.



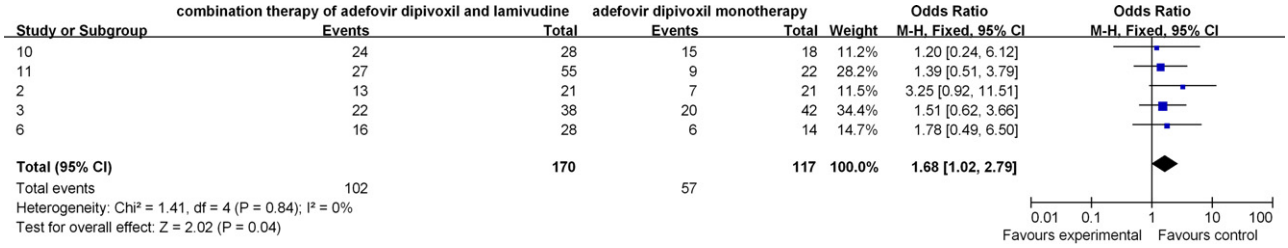
Appendix 4. Forest plot for biochemical response after >12 months of therapy.



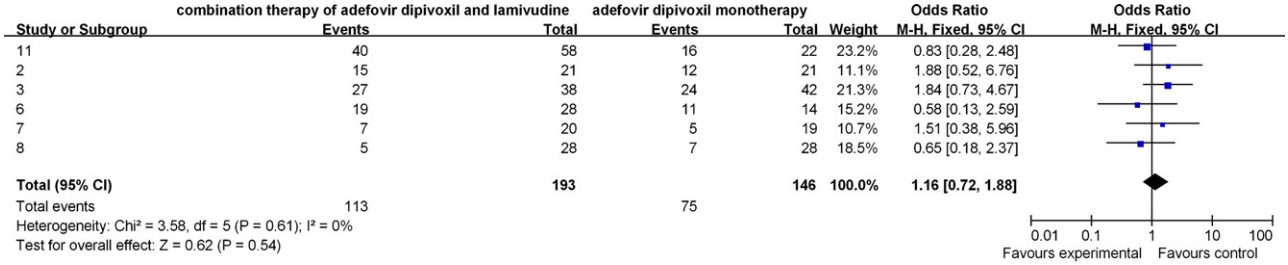
Appendix 5. Forest plot for virological response after 3 months of therapy.



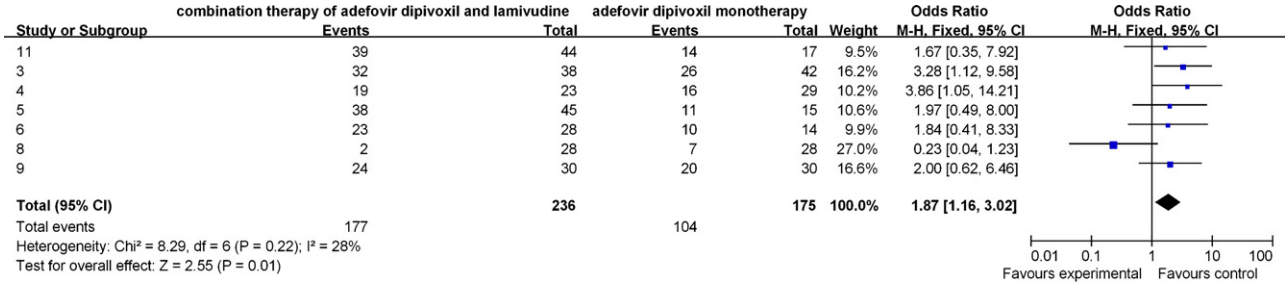
Appendix 6. Forest plot for virological response after 6 months of therapy.



Appendix 7. Forest plot for virological response after 12 months of therapy.



Appendix 8. Forest plot for virological response after >12 months of therapy.



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